Viruses and hepatocellular carcinoma

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Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are important worldwide problems. It is believed that 300 million people have been exposed to hepatitis B.¹ In Europe, based on a carrier rate in blood donors of 0.1% and a population of 400 million, it is estimated that four million have been exposed to hepatitis C. Hepatocellular cancer is estimated to have an incidence of between 250,000 and 1.2 million per year worldwide.² It is the seventh commonest cause of cancer in men, and most show evidence of HBV or HCV infection.

The relation of the virus to the development of hepatocellular carcinoma (HCC) is through chronic hepatitis and cirrhosis (Fig 1). Almost all patients with virus related HCC have an underlying cirrhosis. The hepatocyte necrosis and mitosis of chronic hepatitis favour nodular regeneration which, in appropriate circumstances, is followed by hepatocyte dysplasia and carcinoma.³ Although nodular regeneration and cirrhosis remain the most important antecedents, the tumour can develop in the absence of cirrhosis. In this case, and by analogy with the HBV-like woodchuck chronic hepatitis, necroinflammatory activity may be an important requisite.⁴

**Hepatitis B virus infection and hepatocellular carcinoma**

There is an undoubted association between hepatitis B virus infection and the development of hepatocellular carcinoma. The geographical distribution of those affected is related to the prevalence of the HBV carrier state in that area. Chronic carriers of HBV are at greater risk of HCC than the general population. Hepadna viruses, such as the woodchuck hepatitis virus, are also associated with hepatocellular carcinoma. Hepatitis B viral DNA has been found in the tumour tissue.

Carcinogenesis is a multistage process in which both virus and host play a part.⁵ The essential end result is the disorganisation and rearrangement of hepatocyte DNA (Fig 2). The molecular mechanism for the postulated hepatocarcinogenic role of HBV is not known. During the course of HBV, the virus becomes integrated with host chromosomai DNA but the method by which this leads to cancer is uncertain. Integration is accompanied by chromosomal deletions and translocations, which effect cell growth and differentiation (insertional mutagenesis). The deletions are not related to the sides of integration, however, and in 15% of cancers, integrated sequences are not found in the tumour.⁶ In the human HCC, the semirandom integration of HBV DNA into the host genome has not been associated with the overexpression of a particular proto-oncogene or with deletion of a specific region of the genome harbouring a potential anti-oncogene.⁷ No consistent pattern of integration has emerged and the viral genome may integrate in different sites in tumours from different subjects.

The hepatitis B X antigen (HBx) has been suggested as a transactivator increasing the rate of transcription of oncogenes.⁸ The pre-S HBV envelope protein may accumulate in toxic amounts sufficient for carcinogenesis. Thus in transgenic mice, overproduction of HBV pre-S, results in severe hepatic inflammation and regeneration, which is followed by neoplasia.⁹ Dysregulation of HBV envelope expression might be a consequence of integration.

Tumour suppressor genes located on chromosome 17 have been associated with HCC. This chromosomal translocation is associated with HBV DNA integration. Thus tumour suppressor genes, such as the P-53 oncogene on chromosome 17 may be a crucial step in HBV related hepatocarcinogenesis.¹⁰ Loss of heterozygosity on chromosomes 10 q, 18 p, and 22 q have been reported with hepatocellular carcinoma in Japanese patients and cited as possible candidates for tumour suppression genes.¹¹

![Figure 1: Stages in hepatocellular carcinogenesis.](image)

![Figure 2: Multiple factors in virus associated hepatocellular carcinoma culminating in disorganised hepatocellular DNA and cancer.](image)
Transforming growth factor α may be a cofactor in some cases. It is expressed at a high value in 80% of human HCC.12 Histochemistry shows that it is localised with HBsAg to the same hepatocyte but not in the cancer cell.

Chronic hepatitis, progressing to cirrhosis, remains the most important precancerous aetiological factor. HBV induces the cancer through integration, transactivation, mutations in tumour suppressor genes and increases in transforming growth factor α.

**Hepatitis C virus**

The most serious complication of HCV disease is the development of hepatocellular cancer. There are geographical differences in the aetiological importance of HCV in HCC. The association seems to be strongest in carriers where the prevalence of HBV is low, for instance, Europe or Japan.13 It is of comparatively minor epidemiological importance in areas such as Hong Kong, where HBV infection is overwhelming.14 Tumours related to HCV tend to be multifocal and diagnosed late.

In contrast with HBV, HCV is an RNA virus that lacks a reverse transcriptase enzyme and does not integrate into the host genome. The mode of carcinogenesis is uncertain, but is presumably through cirrhosis.15-17 HCV genomes, however, can be detected in the tumour and surrounding liver tissue.18

The low prevalence of HCV related HCC in the United States compared with Japan might be related to the age of the patient. It is estimated that HCC develops some 10 to 29 years after infection.19 The Japanese probably acquired HCV infection in early childhood through unsterile syringes and injections. The Americans largely contracted it in adult life from drug abuse or infected blood transfusions. They must wait for the full impact of HCV related HCC to strike them.

**Prevention of virus related hepatocellular carcinoma** (Table I)

This depends on control of HBV and HCV. Universal vaccination against HBV will ultimately eliminate the disease. Unfortunately there is no vaccine against HCV and there is none on the immediate horizon.

Screening blood donors for HBV and HCV will eliminate post-transfusion hepatitis. HBV infections will be reduced by changes in lifestyles, such as safer sex, elimination of drug abuse, and the use of sterile syringes and needles, not only for drug abusers but for treatment in developing countries. Hopefully, effective antiviral treatment will prevent chronic hepatitis developing to cirrhosis, the precursor of HCC.

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<td>Universal vaccination against HBV</td>
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<td>Screening blood donors</td>
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<td>Changing life styles</td>
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<td>Sterile syringes and needles</td>
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<td>Antiviral treatment to prevent cirrhosis</td>
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**Prognostic and risk factors**

The time lag between exposure to the virus and tumour development can vary from a few years to many decades.20 In many patients, particularly the Japanese and the Italians, hepatocellular cancer grows slowly and may be asymptomatic for years.

The growth rate of the tumour varies greatly. In the case of asymptomatic Italian patients, the tumour volume doubling time varies from 1 to 19 months with a mean of six months.20 21 Doubling time correlates with survival. Hepatocellular carcinoma in Africans is much more rapidly growing.22 The reasons are speculative, perhaps genetic, perhaps related to underlying malnutrition, to cofactors such as aflatoxin or perhaps to late diagnosis in an itinerant African mine worker.

Age of the patient is an independent risk factor for HCC in both HCV and HBV positive patients.23 Severity of liver disease correlates with the chances of developing hepatocellular cancer.23 In a total of 917 Japanese patients studied between 1987 and 1991, the three year cumulative risk of liver cancer was 12.5% in well compensated cirrhotic patients compared with 3.8% in those with chronic hepatitis.24 Risk increased almost sevenfold in HBsAg positive patients and fourfold in those who had the antibody to the hepatitis C virus. Continued necrosis of liver tissue (expressed by an increased serum α fetoprotein or transaminase activity and older age) seem to be more significant promoting factors than merely HBV or HCV infective state.

Although cirrhosis is the main risk factor, macro-regenerative nodules (at least 1 cm in diameter) are particularly precancerous.25 26 Nodules having cellular or architectural atypia (small cell dysplasia and abnormal nuclear ploidy) are particularly indicative of malignant potential in cirrhotic livers.27 A macro-regenerative nodule can contain a hepatocellular cancer in a non-cirrhotic liver.28 An increased serum α fetoprotein at presentation predicts the eventual development of hepatocellular cancer at follow up.20 23 The role of cofactors in increasing the risk of hepatocellular cancer in virus infected patients is uncertain. They probably function only by facilitating the development of cirrhosis. In endemic areas, the chances of being infected with both HCV and HBV is increased.17 It is uncertain whether this coinfection increases the likelihood of the development of HCC. Originally, in high endemic areas, progression from chronic hepatitis to cirrhosis and to HCC was thought to be increased by double infection. This was based on HCV antibody testing, largely by first generation methods. When specific viral markers (HCV RNA and HBV DNA) were measured in Spain, only nine of 63 patients with HCC were coinfected by HBV.29 In an Italian study, HCV seemed to act independently of HBV as a risk factor for HCC in patients with cirrhosis.16 In an Italian study, alcohol abuse did not seem to increase the risk of hepatocellular
carcinoma in patients with HCV related cirrhosis. This is in contrast with a Japanese report, where past alcohol consumption was an independent predictor for the appearance rate of hepatocellular carcinoma in HCV antibody positive patients but not in those positive for hepatitis B surface antigen.

**Screening for hepatocellular carcinoma**

The one year survival of untreated patients, with well compensated liver disease (Child's grade A) and having an asymptomatic HCC is 96% at one year whereas the one year survival of symptomatic patients is only 40%. Underlying liver disease plays a key part in the probability of longterm survival. Screening is therefore indicated for early detection of a small HCC at a time when the patient is asymptomatic. The success of screening is related to the growth rate of the tumour. It will clearly be more effective with the Japanese slow growing tumour than with the South African rapidly progressive one.

Screening is indicated for patients at high risk of developing HCC. These are men, HBSAg or anti-HCV positive, more than 40 years old, and with chronic liver disease, especially with cirrhosis and large macro-regenerative nodules. Ultrasound will detect a tumour greater than 2 cm diameter with 90% success. This is usually followed by directed fine needle biopsy. This technique carries little risk of disseminating the tumour to subcutaneous tissues or skin. Guided biopsy must also be used to obtain specimens from non-tumorous tissue to determine the presence or absence of a concomitant cirrhosis and its activity.

Serum α fetoprotein estimations should be performed at four to six month intervals, particularly in those who have an initially increased concentration or where macro-regenerative nodules have been detected. Serum α fetoprotein is not as reliable as ultrasound as concentrations may be normal or only modestly increased in those with small tumours.

There are geographical differences in the reported success rates of screening. They are high in areas such as Japan where tumours are small and often encapsulated. In South Africa, tumours are rapidly growing and aggressive and screening is of little value. Europe seems to be in an intermediate position. A large Italian study, screening cirrhotic changes failed to show increases in the rate of detection of preventable, curable hepatocellular tumours although screening at one year intervals may have been too infrequent. In a prospective study carried out in Alaskan natives, 20 patients with HCC were identified by ultrasound, some at an early enough stage to permit successful hepatic resection.

Economics play a part in planning screening programmes. In Japan, such procedures as ultrasound and α fetoprotein estimations are routinely available at no cost to the patient. This is clearly not so in most other parts of the world. The prognosis for HCC is so poor that where cost is an important consideration, there is probably a reluctance to screen. After local treatment, such as resection, the cirrhosis persists. This is a pre-neoplastic state, so that HCC may arise in cirrhotic nodules one after another. Transplantation may be an option in early cases, but donor livers are never likely to be in adequate supply. There is no firm consensus that screening reduces the death rate of HCC.

**Management**

Accurate localisation is essential, particularly if surgery is planned. This is best done by computed tomography with or without angiography. It may be combined with iodised oil (lipiodol), which has an avidity for HCC and which is injected into the hepatic artery; abdominal computed tomography is performed two weeks later. The lipiodol is taken up by the tumour or tumours and 96% are detected. The procedure, however, does add to the complexity of the diagnosis and is not always necessary. Serum markers for HBV and HCV are performed, but there is little difference in management whether or not these are positive and the HCC is virus related.

Successful local resection of the tumour depends on size (less than 5 cm in diameter), position, particularly in relation to large vessels, presence of satellite lesions, and of a capsule and of a number of lesions (Table II). It also depends on the age and general condition of the patient, the grade of hepatic decompensation (Child's grade) and the presence of extrahepatic metastases. Improved results for resection have followed better knowledge of the segmental anatomy of the liver and hence better localisation of the tumour. Also this has followed the use of intraoperative diagnostic ultrasound. In Spain, survival increased from 12-4 months in untreated controls to 27-1 months in those with resected tumours, and results were even better for tumours less than 5 cm. 20 patients with HCC were resected. In a recent study from Japan of 229 consecutive patients having liver resection for HCC during 11 years, the 5 and 10 year survivals were 26-4% and 19-4% respectively. Recurrence outside or inside the new liver can be expected within the first two years. These recurrences merit consideration of further surgery, which gives better results than palliation.

Hepatic transplantation gives disappointing results because of recurrence of the hepatis virus infection and more particularly recurrence of tumour. Survival time is surprisingly short after recurrence. Mean tumour doubling time is considerably shortened compared with HCC recurrence after hepatic resection. This is presumably related to the effects of the immunosuppressive treatment given to prevent rejection. Cirrhotic patients with pre-transplant HBEAg or HBV DNA show particularly early recurrence of

<table>
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<th>Size &lt;5 cm</th>
<th>Satellite lesions and capsule</th>
<th>Number</th>
<th>Position</th>
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<th>Age and general condition</th>
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<td>TABLE II</td>
<td>Factors in resection for HCC</td>
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both viral infection and tumour. In the United States, national funding will not cover the costs of transplants for HCC. Cures have been recorded, however, where the tumour is an incidental finding at the time of transplantation for end stage cirrhosis.41 Tumour obliteration may be attempted locally. In general, those selected tend to be unsuitable for resection or transplantation and hence are poorer risks and consequently the results are worse.

Using ultrasound guidance, absolute alcohol may be introduced directly into the tumour.45 It is especially useful for tumours less than 3 cm in diameter. The one year survival for Child’s A and B grades is 87% and at two years it is 70%.46 The alcohol injections are repeated two to three times a week until the tumour is obliterated. The objective of injections may be palliative or an attempt to cure.47 Results of 98 Japanese patients, where the ethanol injection was to cure showed necrosis of the tumour, reduction in α fetoprotein, and improved arteriographic appearances.47 One, two, three, four, and five year survival rates were 85%, 70%, 62%, 52%, and 52%, and the one, two, three, four, and five year recurrence rate was 26%, 28%, 51%, 60%, and 60%. The recurrences usually originated from new lesions in different parts of the liver. Other local procedures include ultrasound guided cryosurgery.48 49 Chemoembolisation via the hepatic artery may be performed using lipiodol tagged with doxorubicin or113 iodine.50 Results have not been fully assessed, but in one study, surgery offered more favourable results in patients with early stage HCC.51 Local procedures are particularly useful for multiple tumours. They may be performed before resection. All are followed by a reaction with pain, fever, leucocytosis, and a rise in serum transaminase activities.

They all leave a rim of tumour tissue, which is not necrosed. After two to three years, 54 to 66% will have developed new lesions whatever the treatment. In a large trial of 123 patients with stage I HCC, usually with cirrhosis, all treatments increased the probability of survival.52 Results, however, did not differ between resection, liver transplantation, and transcatheter oil embolisation. Rarely have the various procedures been subjected to prospective clinical trials. Results are compared with historical controls or no treatment.53 Trials are urgently needed.

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